

Life-threatening pulmonary interstitial lung disease complicating pediatric nonhumoral immunodeficiencies

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Clinical Implications

- Interstitial lung disease in children often indicates a life-threatening primary immunodeficiency disorder and has a poor prognosis without hematopoietic stem cell transplantation. Lung biopsy often provides definitive pathological results that help to direct management decisions.

TO THE EDITOR:

Recurrent acute and chronic lung infections associated with bronchiectasis are a major cause of morbidity and mortality in patients with primary immunodeficiency disorders (PIDs).¹⁻³ In adults, inflammatory interstitial lung disease (ILD) not due to pyogenic infection is found in up to 20% of patients with common variable immunodeficiency disorders (CVID) and can be associated with progressive restrictive lung disease and shortened survival.^{4,5} High-resolution chest computed tomography (CT) scan is the gold standard imaging technique for diagnosing ILD. Where there is doubt about the diagnosis, lung biopsy is recommended.^{1,2} Histology classically shows lymphocytic infiltrates and/or granuloma, which in adults with CVID is termed granulomatous-lymphocytic interstitial lung disease (GLILD).⁶ Although there are reports of ILD associated with a number of monogenic PIDs including cytotoxic T-lymphocyte-associated protein 4, lipopolysaccharide-responsive and beige-like anchor protein (LRBA), recombination-activating gene (RAG1) deficiencies, X-linked inhibitor of apoptosis protein, and chronic granulomatous disease (CGD),^{2,7,8} there are no published series delineating the prevalence, clinical characteristics, histologic features, and management of children with PID and ILD. This retrospective case series aimed to review the genotype and clinicopathological phenotype of children presenting to our tertiary pediatric primary immunodeficiency center at Royal Manchester Children's Hospital, Manchester, United Kingdom, between 2005 and 2018 with ILD and PID who underwent detailed investigations including chest CT scans and in most cases lung biopsy. We hypothesized that ILD in children often indicates life-threatening primary immunodeficiency disease and has a poor prognosis without hematopoietic stem cell transplantation (HSCT).

The case note review was part of a Natural History and Causes of CVID study approved by the Local Research Ethics Committee (03/ST/016). The demography, immunology, histology,

and genetic screening of 9 patients (0.9%) with PID and ILD of 1,034 new pediatric referrals to our service because of recurrent, unusual, or serious infections or inflammatory diseases were collated (Table I, Figure 1, and Online Repository at www.jaci-inpractice.org). This series of patients includes all but one patient known to Departments of Paediatric Histopathology, Immunology, and Respiratory Medicine who had lung biopsies that demonstrated ILD associated with lymphocytic infiltration and/or granuloma formation.

Seven of the 9 patients were males. Seven were Asian. All presented with a chronic cough and breathlessness suggestive of recurrent chest infections or asthma. In all but one case in which there was a family history of PID, it was the onset of chest symptoms that prompted a search for an underlying immunodeficiency disorder. A genetic diagnosis was confirmed in 7 patients. Three children had a primary neutrophil immunodeficiency (2 p40phox CGD and 1 G6PC3 deficiency), and 4 a primary T-cell immunodeficiency (*RAG1*, *STK4*, *LRBA*, *ITK*). Whole exome sequencing of an eighth patient with pulmonary EBV-driven lymphoproliferative disease (LPD) uncovered a potentially pathogenic variant in a gene involved in T-cell signaling, and further experiments to confirm the functional relevance of this novel finding are in progress. The ninth patient died from pulmonary hemophagocytosis lymphohistiocytosis (HLH) in 2006. Limited candidate gene screening at the time was negative, and there was insufficient DNA available for subsequent whole exome sequencing. The median age of onset of chest symptoms of the 9 patients was 12 months. Except for 1 male who presented in the second year of life with *RAG1*-deficient severe combined immunodeficiency (SCID) and died of progressive multifocal leukoencephalopathy, and a teenage boy who died of fulminant pulmonary HLH, the remaining 7 patients were alive 12 months to 14 years after HSCT.

Lung biopsies assisted to direct clinical management (Figure 1). Tuberculosis and fungal infections were excluded, allowing for the discontinuation of antimicrobials. No evidence of vasculitis was found in any of the patient's biopsies. Although granulomata were only seen in the patients with CGD, a number of the patients had a prominent histiocytic (CD68) infiltrate. This is in keeping with the lung histology of GLILD in adults with CVID, which is characterized by loose, more diffuse collections of histiocytic and lymphocytic infiltrates rather than well-defined clusters of histiocytes and multinuclear giant cells typical of sarcoidosis.⁵ In the 3 patients with primary neutrophil immunodeficiencies and the patient with the LRBA deficiency, lung biopsy confirmed the diagnosis of an inflammatory ILD rather than pyogenic infection, and responded to high-dose corticosteroids before HSCT. In the 4 patients with primary T-cell immunodeficiencies, lung biopsies confirmed EBV-driven LPD, allowing focused treatment with rituximab ± EBV-directed cytotoxic T-cells or chemotherapy. The lung biopsies of the teenager who died showed a mixed histiocytic, T- and B-lymphocytic infiltrate, and evidence of hemophagocytosis. Infections including EBV-driven LPD and vasculitis were excluded.

In conclusion, this is the first case series to delineate the variation in genotype and the frequent life-threatening clinical

TABLE I. Patient characteristics

Patient number	Gene defect	Dx*	Age at onset of chest disease (m)	Age at onset of lung disease Dx (m)	Age at PID Dx (m)	Age at HSC† (m)	Race‡	Gender	Outcome	Hemoglobin (g/L)	Platelets (×10 ⁹ /L)	Lymphocytes (×10 ⁹ /L)	IgM (g/L)	IgG (g/L)	IgA (g/L)	CD4 (×10 ⁶ /L)	CD8 (×10 ⁶ /L)	CD19 (×10 ⁶ /L)	CD56 (×10 ⁶ /L)	Lung histology
1	<i>NCF4</i>	CGD	24	31	36	56	A	f	Alive	119	215	3.04	1.0	12	2.1	1058	933	1415	129	G
2	<i>NCF4</i>	CGD	8	44	56	62	A	f	Alive	125	297	1.88	0.98	13.8	1.76	906	766	3755	32	L
3	<i>G6PC3</i>	G6PC3	1	97	112	142	A	m	Alive	128	58	0.49	0.44	17.9	0.32	339	271	164	23	L
4	<i>LRBA</i>	LRBA	3	138	138	144	A	m	Alive	80	173	1.8	1.27	7.65	0.48	495	282	794	39	L
5	<i>ITK</i>	CID	7	10	1	12	A	m	Alive	124	351	3.11	1.32	6.6	0.87	2072	978	993	162	E-L*
6	<i>STK4</i>	CID	12	12	142	144	A	f	Alive	105	348	1.30	1.06	31.1	4.89	100	570	270	200	E-L
7	<i>RAG1</i>	CID	14	22	27	—	O	m	Died	111	510	0.17	1.56	6.82	<0.1	19	50	37	221	E-L
8	?	CID	48	69	—	98	A	m	Alive	138	340	3.8	3	21	30	800	1887	283	69	Φ
9	?	HLH	168	180	—	—	C	m	Died	97	60	0.41	5.02	11.2	1.22	260	200	60	20	L

CGD, Chronic granulomatous disease; CID, combined immunodeficiency; CT, computed tomography; Dx, diagnosis; HLH, hemophagocytosis lymphohistiocytosis; HSC†, hematopoietic stem cell transplantation; ITK, IL-2 inducible T-cell kinase; LRBA, lipopolysaccharide-responsive and beige-like anchor protein; *NCF4*, neutrophil cytosolic factor 4; PID, primary immunodeficiency disease; *G6PC3*, glucose-6-phosphatase catalytic subunit 3 deficiency; *LRBA*, lipopolysaccharide (LPS)-responsive and beige-like anchor protein deficiency; *CGD, chronic granulomatous disease; CID, combined T/B-cell immunodeficiency; †A, Asian; C, Caucasian; O, Other. Lung histology: noncaseating granuloma (G), lymphoid hyperplasia (L), lymphoma (L*), EBV (E), Φ—EBV-lymphoproliferative disease diagnosed after finding EBV from sputum, nodular shadowing on CT scan images and response to rituximab.

phenotype of children with ILD complicating PID. Lung biopsy often provides important information that helps to direct management decisions, not only by ruling out fungal and mycobacterial infections and vasculitis, but also in tailoring therapy based on the presence of inflammatory infiltrates or EBV-driven LPD. Diagnosis of the underlying PID is challenging, as patients may not only present with classical phenotypes such as EBV-positive ILD secondary to IL-2 inducible T-cell kinase deficiency, but also with unusual manifestations, for example, “late-onset” SCID, or p40phox CGD where the standard dihydrorhodamine test may be normal.^{8,9} HSCT can be life-saving and should be considered as a definitive, curative therapeutic option. It is however important that HSCT is carried out by experienced transplant physicians, as the post-transplant course can be complicated by severe inflammation of the lungs, liver, and gut in this group of patients.

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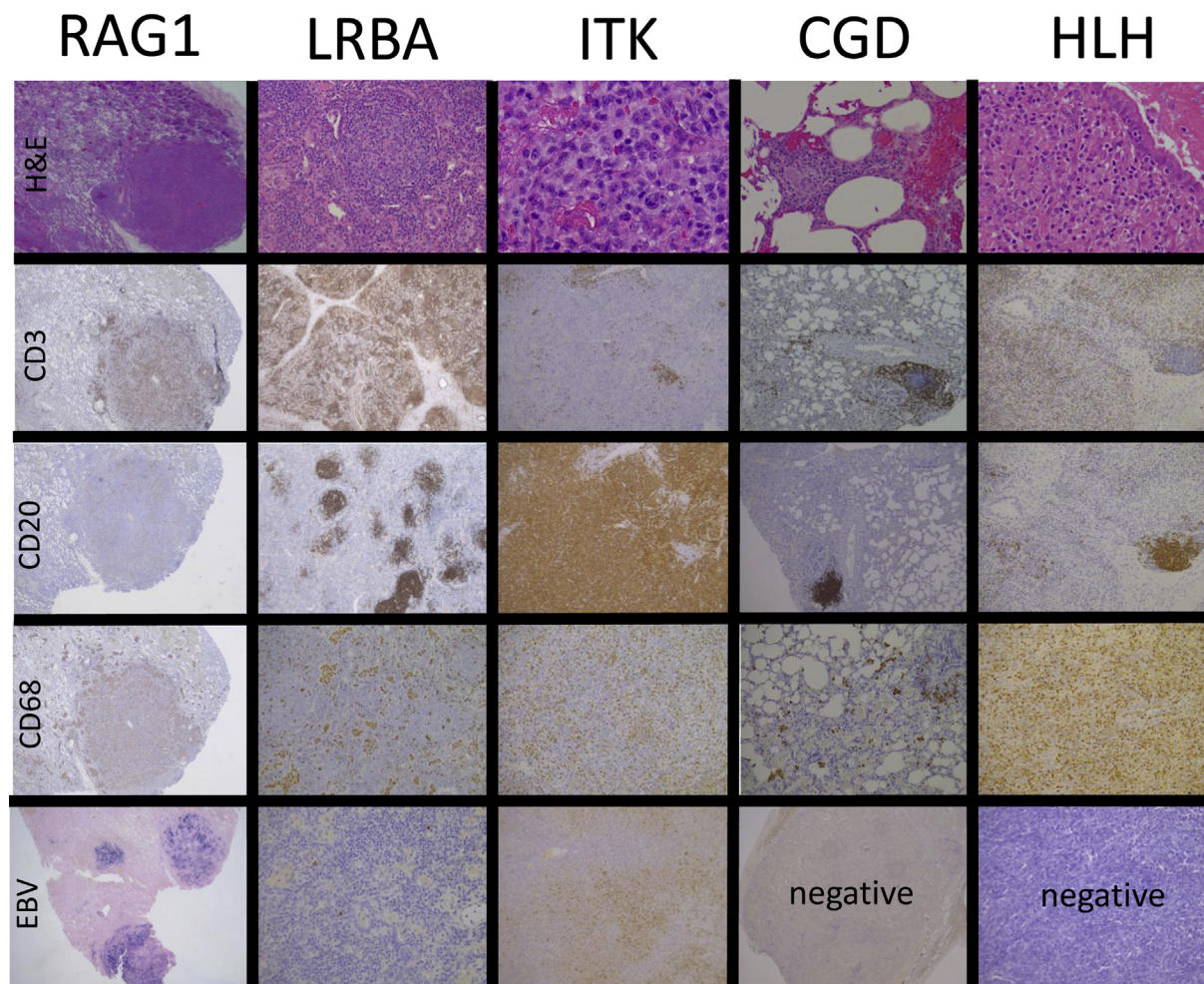


FIGURE 1. Characteristic lung biopsies of different PID associated with interstitial lung disease. Panels (top to bottom) show hematoxylin & eosin (H&E), CD3 (T cells), CD20 (B cells), CD68 (histiocytes), and EBV *in situ* hybridization (EBV) for each condition. *CGD*, Chronic granulomatous disease; *HLH*, hemophagocytosis lymphohistiocytosis; *ITK*, IL-2 inducible T-cell kinase; *LRBA*, lipopolysaccharide-responsive and beige-like anchor protein; *PID*, primary immunodeficiency disorder; *RAG1*, recombination-activating gene.

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CLINICAL CASE VIGNETTES

High-resolution chest computed tomography [CT] scans are shown in [Figure E1](#).

Patient 1

A 4-year-old Pakistani girl presented at the age of 2 years with a chronic cough and clubbing, associated with cervical lymphadenopathy and hepatosplenomegaly. Parents were first cousins. There was no family history of chest problems or tuberculosis. A chest x-ray showed bilateral, multinodular shadowing. Chest CT scan confirmed patchy infiltrates in the right and left lower lobes, but no bronchiectasis. Hilar lymphadenopathy was noted, particularly on the right (7×10 mm). Bronchioalveolar lavage revealed no microbes. Lymph node biopsy showed granulomatous inflammation without caseation. Stains for mycobacteria and fungi were negative. Because of the chronic unremitting nature of the lung disease, a lung biopsy was performed, which showed granulomatous lymphocytic infiltration with no organisms identified.

Standard dihydrorhodamine test with phorbol 12-myristate 13-acetate (PMA) was normal, but stimulation with *Escherichia coli* was reduced. Gene sequencing revealed a homozygous c.118-1G>A splice variant in the *NCF4* gene consistent with p40phox chronic granulomatous disease (CGD).⁸ Parents were both heterozygous carriers. The symptoms did not respond to antimicrobials and could only partly be controlled with intermittent pulse intravenous methylprednisolone.

In view of the diagnosis of CGD and her ongoing inflammatory lung disease, she underwent matched-sibling hematopoietic stem cell transplantation (HSCT) at the age of 3 years. Post-transplant course was complicated by mild veno-occlusive disease treated with defibrotide, followed by fulminant inflammatory disease of her gut, liver, and lungs, complicated by pulmonary hemorrhage, requiring high-frequency oscillatory ventilation in intensive care. The lung disease was brought under control with anti-TNF therapy and extracorporeal photopheresis. Twelve months after transplant she developed autoimmune thrombocytopenia, which responded to rituximab. Eighteen months after transplant, her condition is stable and systemic immune suppression has been discontinued. Peripheral leukocytes are 100% donor.

Patient 2

A 7-year-old Pakistani girl presented with a history of chronic chest symptoms going back to when she was 8 months old. She had a chest deformity, clubbing, and oxygen saturations in air of 88%. Her growth and development were delayed and she had intermittent fevers and an iron deficiency anemia. Parents were first cousins. No pathogens had been isolated from her chest. Because of wheeze and breathlessness, she had been treated with recurrent courses of oral prednisolone. Chest x-ray and CT scan showed hilar lymphadenopathy and bilateral patchy shadowing and nodules especially in both lower lobes. There was no bronchiectasis. Lung biopsy showed interstitial inflammation with lymphoid follicle formation. There was alveolar remodeling, prominent type 2 pneumocyte hyperplasia, and abundant intra-alveolar proteinaceous exudates.

Dihydrorhodamine test with PMA was normal, but stimulation with *E. coli* was reduced. Gene sequencing revealed a

homozygous c.32+2T>G variant in *NCF4* consistent with p40phox CGD. Both parents were found to be carriers. Her inflammatory lung disease was only partly controlled with pulse methylprednisolone therapy. She therefore underwent matched unrelated HSCT at the age of 5 years. Three months after transplantation, she developed lung EBV LPD, which was treated with rituximab. Four months after transplant she developed a central line infection complicated by *Klebsiella pneumoniae* septicemia, cardiac tamponade, and cardiogenic shock requiring intensive care. Two years after transplantation she is now well and off all medication.

Patient 3

A 12-year-old Pakistani boy suffered from episodes of cough, wheeze, and breathlessness from 1 month of age. He had been treated with multiple courses of antibiotics, inhaled steroids, nebulized bronchodilators, and oral prednisolone. He also had chronically loose stools. His parents were first cousins. He was referred to our primary immunodeficiency center at the age of 9 years after moving to the United Kingdom. He had been diagnosed with a congenital neutropenia at the age of 6 years and started on regular G-CSF, although continued to have persistent cough and dyspnea, with poor exercise tolerance requiring supplementary nighttime oxygen. FEV₁ and forced vital capacity were 30% of predicted. Stool culture, bronchoscopy, and bronchoalveolar lavage revealed no pathogens. Mantoux and Quantiferon tests were negative.

High-resolution chest CT scan showed air trapping and nodular opacities in the left lower lobe, with only mild basal bronchiectasis. Lung biopsy showed peribronchial mononuclear infiltrate with occasional lymphoid nodules with no granuloma, fungi, or mycobacteria. There was no fibrosis or pulmonary hypertensive changes. Gut biopsies showed inflammation with cryptitis, crypt abscesses, and inflammatory infiltrate throughout the colon but no granuloma. There were also patchy inflammatory changes in the esophagus, stomach, and terminal ileum.

In view of his congenital neutropenia, symmetrical growth retardation, cryptorchidism, and distended veins on his anterior chest, genetic testing was performed that confirmed a homozygous frameshift c882_903 duplication in the *G6PC3* gene. Because of frequent hospital admissions for his lung disease and poorly controlled inflammatory bowel disease, he underwent matched unrelated HSCT. Fifteen months after transplant, he is now able to scooter along the flat and not needing supplementary oxygen. His stool frequency has also decreased. Post-transplant immune suppression has been discontinued with 100% donor engraftment.

Patient 4

An 11-year-old Indian boy presented in infancy with chronic watery diarrhea due to an autoimmune nongranulomatous colitis. He was treated for 4 years with corticosteroids, to which azathioprine was added. His parents were first cousins. At the age of 7 years, he developed generalized atopic dermatitis, and at 8 years, cervical lymphadenopathy, splenomegaly, chronic urticaria, a Coombs positive hemolytic anemia, and idiopathic thrombocytopenia purpura with epistaxis, which only partly responded to corticosteroids, methotrexate, and intravenous rituximab. At the age of 10 years, while on the methotrexate (10 mg/m²/week), he developed interstitial lung disease (EBV positive by PCR on sputum but not blood) with fevers and signs of

respiratory distress. High-resolution chest CT scan showed confluent dense consolidation in both lower lobes, multiple areas of hazy nodular, ground glass changes, and hilar lymphadenopathy. Lung biopsy showed a diffuse, reactive lymphoid hyperplasia with lymphoid follicle formation. At the same time, his autoimmune cytopenias became more difficult to control. His lung disease and cytopenias only partly responded to rituximab, and required high-dose systemic corticosteroids.

Whole exome sequencing revealed a homozygous c.5770_5776 deletion in the *LRBA* gene. Both parents were carriers. As there were no suitable matched-sibling or unrelated donors, he underwent a maternal haploidentical peripheral blood TCR $\alpha\beta$ -depleted HSCT with reduced intensity conditioning. His post-transplant course was uncomplicated. Four years after transplant, he off all medication and has 100% donor engraftment. His chest disease, autoimmune enteropathy, and cytopenias have resolved. Because of proteinuria, he investigated and diagnosed with diffuse mesangial sclerosis, which is currently not progressive and he has normal renal function and no proteinuria.

Patient 5

Prompted by a family history, a 15-year-old boy diagnosed with a homozygous c.626G>A *ITK* deficiency at the age of 1 month. HSCT was also delayed because of Hirschsprung's disease requiring surgery in the neonatal period and the difficulty finding a suitable donor. At the age of 7 months, EBV viremia was noted and chest CT scan showed widespread bulky masses throughout both lungs. The largest of these replaced most of the right upper lobe. There were multiple smaller nodules scattered throughout both lungs. Lung biopsy showed replacement of normal parenchyma with an EBV-driven diffuse large B-cell lymphoma. He was treated with rituximab and the UK CCSG NHL901 chemotherapy protocol, followed by a single allelic A mismatched-related donor transplant. He remains well off all therapy 14 years after HSCT.

Patient 6

A 16-year-old Asian girl presented at the age of 3 years with a history of recurrent infections from 14 months, when she developed viral croup requiring ventilation and cryptosporidial diarrhea. Over the next few years, she suffered from recurrent *Streptococcus pneumoniae* pneumonia and ear infections, as well as recurrent thrush, molluscum contagiosum, and herpes gingivostomatitis requiring intravenous acyclovir. She had a chronic productive cough, which did not respond to asthma inhalers. Examination revealed tachypnea and oxygen saturations in air of 94%, a discharging left ear, and oral thrush.

Investigations showed a CD4 lymphopenia but raised reactive serum immunoglobulins and protective vaccine antibody responses. HIV screen was negative. EBV was detected in the blood by PCR. Chest CT scan showed multiple small nodules of different sizes throughout both lungs and no bronchiectasis. Lung biopsy showed a B-cell infiltrate positive for EBV. Her lung EBV-lymphoproliferative disease was treated with rituximab. Parents were first cousins and 2 other sisters also had a CD4 lymphopenia associated with opportunistic infections, both dying of infectious complications after HSCT.

The patient was initially treated conservatively with prophylactic valaciclovir, cotrimoxazole, and fluconazole. However, at the age of 12 years, she developed an extra-nodal B-cell lymphoma within her left submaxillary salivary gland with evidence of

paraprotein bands in her blood. Whole exome sequencing confirmed an *STK4* c.442C>T gene variant in the patient and both her affected siblings. Parents were heterozygous carriers. Because of the progressive disease, the patient underwent matched-sibling HSCT. Post-transplant course was complicated by cytomegalovirus (CMV) reactivation with diarrhea, which responded to ganciclovir. The patient is currently well 4 years after HSCT.

Patient 7

A Turkish Cypriot boy presented at the age of 20 months with a history of recurrent cough, wheeze, and progressive dyspnea, which started at 14 months. He had been admitted to hospital 5 times, once to the pediatric intensive care with "asthma," which only partly responded to inhaled bronchodilators and short courses of oral prednisolone. There was no consanguinity or significant family history.

Blood tests showed persistent lymphopenia ($0.5 \times 10^9/L$) with CD3^{low}CD19^{low}CD56^{normal} lymphocyte subsets. Serum IgA was undetectable but IgM and IgG were normal, as were vaccine responses to tetanus, *Haemophilus influenzae* type B, measles, and 4 of 12 pneumococcal serotypes. Chest CT scan showed extensive nodules in both lungs, particularly in the lower lobes. Respiratory secretions at bronchoalveolar lavage were positive for EBV by PCR. Lung biopsy showed a nodular, T-cell-rich lymphohistiocytic infiltrate with EBV positivity demonstrated by *in situ* hybridization. A diagnosis of lung EBV-driven lymphoproliferative disease was made, and the patient was treated with rituximab and EBV-directed cytotoxic T-lymphocyte infusions. Concurrently, the patient developed a rapidly progressive encephalopathy with hemiplegia and brain stem dysfunction requiring intensive care. Brain magnetic resonance scan was indicative of progressive multifocal encephalopathy. Blood and urine BK, JC, and astrovirus PCR were all negative. The patient deteriorated and died at the age of 21 months. Postmortem was refused. Genetic results received after death showed a homozygous *RAG1* c.2333G>A variant. Both parents were heterozygous carriers.

Patient 8

A Pakistani boy presented at the age of 4 years with an 8-week history of fevers and weight loss and hepatomegaly. Chest x-ray showed extensive consolidation and chest CT scan showed diffuse interstitial changes with fine reticulation and small nodular opacities in all lobes, particularly the right upper lobe, middle lobes, and left lower lobes. There was no bronchiectasis. He was initially treated for tuberculosis, although there was no evidence of TB on culture, Mantoux, or Quantiferon testing. EBV was identified by PCR from his sputum (log 4.5) and blood (log 4.1), although EBV IgM and IgG were both negative. Lymphocyte subsets were normal and serum immunoglobulins were all raised. Whole exome sequencing was performed and no variants in known genes causing PID were revealed, but a potentially pathogenic mutation in a novel gene has been identified and functional tests are ongoing.

The EBV lymphoproliferative disease was successfully treated with rituximab, and thus although lung biopsy had been considered to rule out lymphoma, it was not performed. He underwent a matched unrelated HSCT and remains well and asymptomatic 2 years after transplantation.

Patient 9

A previously well white European male presented in 2005 at the age of 14 years with night sweats, vomiting, anorexia, and weight loss but no diarrhea. There was no consanguinity or significant family history. An episode of chickenpox at 3 years was no more severe than normal. Endoscopy showed active gastritis (*Helicobacter pylori* negative) with no evidence of inflammatory bowel disease. At 15 years, after viral respiratory illness (which other family members also suffered), he developed a cough, progressive breathlessness, bilateral pleural effusions, and respiratory failure. Laboratory investigations showed a generalized lymphopenia ($0.53 \times 10^9/L$), thrombocytopenia, and hyperferritinemia (5636 $\mu g/L$), but normal mitogen responses, serum immunoglobulin concentrations, serum angiotensin-converting enzyme, and neutrophil oxidative burst test.

Chest CT scan showed extensive reticulonodular interstitial shadowing, particularly in both lower lobes, with relative sparing of

the upper lobes. Lung biopsy demonstrated an intra-alveolar histiocytic and T-cell infiltrate with follicle formation. There were no granulomata. EBV, fungi, and acid-fast bacilli were absent.

His lung disease did not respond to pulse methylprednisolone or methotrexate. He was ventilated in intensive care, but died 1 week later from progressive lung failure. Postmortem histology of the lungs showed extensive infiltration of macrophages and lymphocytes, with diffuse alveolar damage and hemorrhage. There was no evidence of infection, vasculitis, or granuloma. No EBV or CMV, or acid-fast bacilli, was seen. Gut tissue showed no evidence of inflammatory bowel disease. Bone (rib), lung, liver, and lymph nodes all show prominent histiocytes with hemophagocytosis. Candidate ADA/PNP, XAP, and FHLH gene screen was normal, and unfortunately there was insufficient DNA available to conduct whole exome sequencing after the patient's death.

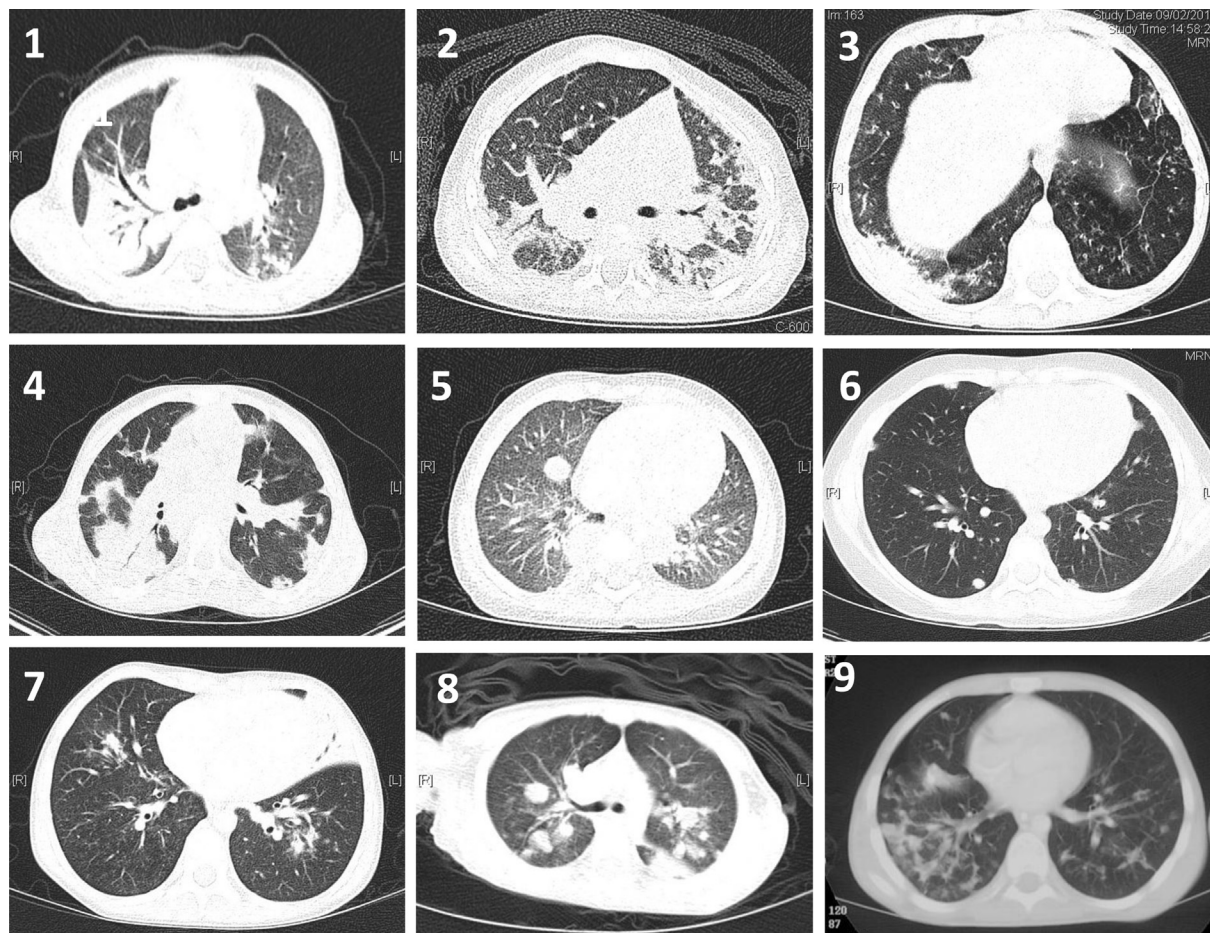


FIGURE E1. Chest high-resolution computed tomography scans. See [Clinical Case Vignettes](#) for description of pathology.

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